

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number
WO 2004/009835 A3

(51) International Patent Classification⁷: **C12Q 1/68**, 1/02,
1/18, C12N 1/20, 15/00, C07H 21/04

J. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **CULLY, Doris, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number:

PCT/US2003/021726

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(22) International Filing Date: 14 July 2003 (14.07.2003)

(25) Filing Language:

English

(81) Designated States (*national*): CA, JP, US.

(26) Publication Language:

English

(84) Designated States (*regional*): European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(30) Priority Data:

60/396,374	17 July 2002 (17.07.2002)	US
60/396,655	18 July 2002 (18.07.2002)	US
60/467,704	2 May 2003 (02.05.2003)	US

Published:

— with international search report

(71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(88) Date of publication of the international search report:
10 September 2004

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **HAMELIN, Michel,**

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR IDENTIFYING CELLULAR GROWTH INHIBITORS

(57) Abstract: The present invention is a method which permits the selective screening for growth-inhibiting substances having a known mechanism of action; i.e., substances which inhibit or otherwise interfere with an enzyme or other gene product whose function is required for the growth or survival of the cell. The method employs cells (e.g., bacterial cells) that contain a nucleic acid fragment that encodes an RNA fragment that can interfere with the expression of a gene product (e.g., an anti-sense RNA that hybridizes to a mRNA), wherein expression of the RNA fragment pre-sensitizes the cell to substances (drugs) that act at the gene product (e.g., a protein or RNA). The cells lose the capability to express the RNA fragment. In the method, the recombinant cells are grown in a nutrient medium in the presence of a test substance under conditions in which expression of the RNA fragment occurs at a level that pre-sensitizes the cell to substances that act at the targeted gene product. The growth conditions are also controlled such that the cells lose the capability to express the RNA fragment. When the test substance is a growth inhibitor that acts on the targeted gene product, the cells lacking the RNA fragment (revertant cells) will have a growth advantage over cells containing the RNA fragment, and the growth of revertant cells will occur. The method of the invention includes monitoring the cell growth for the appearance of revertant cells, which leads to the identification of selective growth inhibitors having a specific mode of action.

WO 2004/009835 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/21726

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68, 1/02, 1/18; C12N 1/20, 15/00; C07H 21/04
US CL : 435/5, 29, 32, 172.3, 252.3, 320.1; 536/24.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DIALOG, WEST, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,821,052 A (CHEN et al) 13 October 1998, see entire document.	1-31
A	DeVito et al. An array of target-specific screening strains for antibacterial discovery. Nature Biotech. May 2002, Vol. 20. No. 5, pages 478-483, see entire document.	1-31

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 November 2003 (03.11.2003)

Date of mailing of the international search report

25 JUN 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Jennifer E. Graser

Telephone No. 571-272-1600